CFAES SCHOOL OF ENVIRONMENT AND NATURAL RESOURCES

The Consequences for Antibiotic Resistance in the Food Chain and Hindrances Induced by Industry Released Metabolites

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INTRODUCTION

Antibiotics can enter the environment through different routes. Antibiotics produced by industry as well as their metabolites are released from plants, hospitals, farms, and households with biological wastes (urine, faeces, sputum, placenta, tissues and organs) or by means of abandoned animals (e.g., cattle in India), stray animals (dogs, pigs, and birds) and open human defecation in slum areas. From the sewage, waste water treatment plants (WWTPs), and surface run off the antibiotics and/or ARG contaminate water and can be dispersed on fields that directly or indirectly enter humans' and animals' food chain systems.

Figure 1. Schematics of major facilitations for antibiotic resistant genes (ARG)

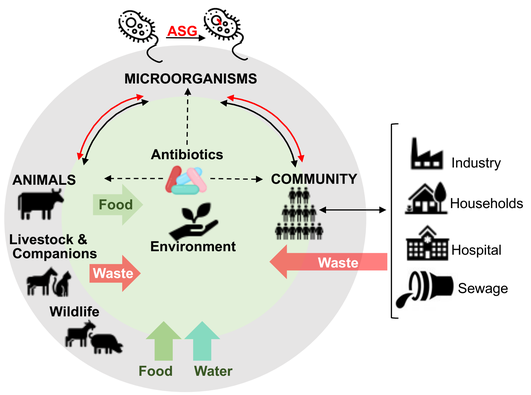
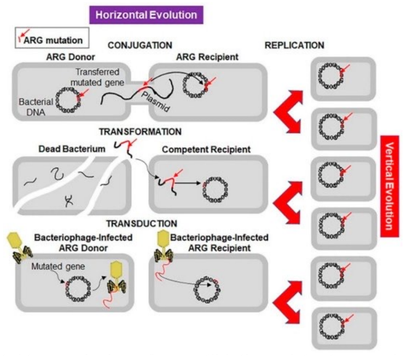


Illustration of the major players involved in exchanges and interaction with both antibiotics and the environment surrounding them to signify the transmission paths in which bacteria are able to develop ARG mutations.

Figure 2. Mechanisms of horizontal and vertical transmission in bacteria



Horizontal transmission of an antibiotic resistant gene depicted by conjugation, transformation, and transduction. The right-hand side of the figure shows the vertical evolution carried out by bacteria replication containing the ARG.

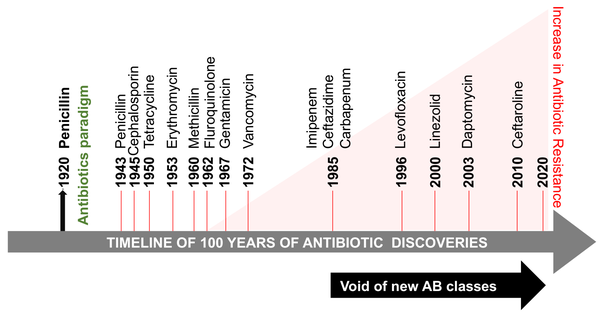
METHODS & ANALYSIS

The method for this study is an analysis of pathways that were previously published. In order to justify the comprehensive and educative nature of this review over two hundred sources were used to build a strong foundation from collection, analyses, and interpretation of both qualitative and quantitative data.

MAJOR FINDINGS

The completed and published review paper highlights many important aspects with regards to nutrition and the environment. Four major aspects of the review that are ideal for discussion would be the void in antibiotics discovery, evolution of antibiotic resistance, antibiotic uses, and others.

Figure 3. Timeline of antibiotic discovery



This figures depicts three major details to note; the beginning of antibiotics development, followed by the discovery of penicillin there is a surge of antibiotics discovery between 60's and 80's, decline in antibiotics development between late 80's and 90's, and the void in new antibiotics classifications.

Table 1. Classification of antibiotic resistance threats

Urgent	Serious
1. *A. baumannii, P. aeruginosa,* carbapenem-resistant	1. *Streptococcus pneumonia,* penicillin-non-susceptible
2. *Clostridium difficile* (CDIFF)	2. *Haemophilus influenzae,* ampicillin-resistant
3. *N. gonorrhoeae*-3rd generation cephalosporin-resistant, fluoroquinolone-resistant	3. *Shigella* spp., fluoroquinolone-resistant
4. Carbapenem- and 3rd generation cephalosporin resistant *Enterobacteriaceae*: *K. pneumonia, E. coli, Enterobacter* spp., *Serratia* spp., *Proteus* spp. and *Providencia* spp., *Morganella* spp.	4. *Enterococcus* spp., vancomycin resistant 5. Multidrug-resistant *Acinetobacter* 6. Drug resistant *Campylobacter* 7.Extended-spectrum β-lactamase producing *Enterobacteriae* (ESBLs) 8. Multidrug-resistant *P. aeruginosa* 9. Drug-resistant non-typhoidal *Salmonella* 10. Drug-resistant *Salmonella serotype Typhi* 11. Drug resistant *M. tuberculosis* 12. Methicillin-resistant *S. aureus* (MRSA)

Microorganisms are able to develop antibiotic-resistant genes to enhance their survival, thus minimizing the treatment options for microbial infections and increasing mortality in human populations. Antibiotic resistance is classified into three categories based on the threat: urgent, serious, and concerning.

Table 2. Mechanism of action of antibiotics

Mechanism of Action	Name of Antibiotic Families
Inhibition of protein synthesis	Tetracyclines, aminoglycosides, streptogramins, ketolides, macrolides, lincosamides, daptomycin
Inhibition of DNA synthesis	Fluoroquinolones, daptomycin
Inhibition of RNA synthesis	Rifampin and other metronidazoles, daptomycin
Inhibition of cell wall synthesis	Penicillins, cephalosporins, carbapenems, monobactams, glycopeptides
Disrupt functions of bacterial outer membrane	Daptomycin, polymyxin B, colistin, and lipopetides
Competitive inhibition of folic acid synthesis	Sulfonamides, trimethoprim

This table contains antibiotics that are routinely prescribed to patients. Even though they have been tested for their efficacy and benefits, the haphazard uses are underestimated, hence the debilitating effects caused antibiotics in humans are often condoned.

Table 3. Antibiotic resistant genes (ARG) in animal production settings

Sl. No.	Bacterial Species	Infection	Antibiotic Resistance Pattern	Sources of Human Infection
1	*Campylobacter* spp.	Gastrointestinal sequelae: Guillain-Barré syndrome	Fluoroquinolones, erythromycin	Food-producing animals (poultry)
2	*Enterococcus* spp.	Sepsis, urinary tract	Aminoglycosides ampicillin vancomycin	Food-producing animals (poultry); People exposed to hospital care, food animals
3	*E. coli*	Gastrointestinal, urinary tract, diarrhoea	Quinolones sulphonamides trimethoprim	Childcare facilities
4	*Salmonella* spp. (non-typhoidal)	Gastrointestinal, diarrhoea	Cephalosporins quinolones tetracyclines	Food-producing animals (pigs, cows, poultry)
5	*S. pneumoniae*	Otitis media, pneumonia, sinusitis, meningitis	Penicillin, macrolides, cephalosporins, tetracyclines	Childcare facilities, paediatric populations
6	*S. pyogenes*	Pharyngitis, impetigo, cellulitis	Macrolides, tetracyclines	Childcare facilities, paediatric Populations, schools
7	*S. aureus*			
	Community-associated	Skin, soft tissue, pneumonia, sepsis	Methicillin, cephalosporins, macrolides	Childcare facilities, injections, drug users
	Healthcare-associated	Endocarditis, pneumonia, sepsis	Methicillin, cephalosporins, quinolones, aminoglycosides, macrolides	People exposed to healthcare facilities such as nursing homes, dialysis, recent surgery or hospitalization
8	*N. gonorrhoeae*	Urethritis, pelvic inflammatory disease	Penicillin, cephalosporins, quinolones	Commercial sex workers

This table illustrates the bacteria present, how it is introduced to humans for infections, and the use of antimicrobial substances in animal production for food.

These findings are significant, especially with the context of an overall 176% increase in antibiotic use was observed during the decade 2000–2010 in Brazil, Russia, India, China, and South Africa (BRICS).

Continuing on this point, animal consumption of antimicrobials in BRICS countries is expected to increase up to 199% by 2030 compared to current use. In human populations its expected growth will be around 113% during the same period. Moreover, with respect to figure 1, it begs to scrutinize the various environments that bacteria can penetrate, interact, proliferate by spreading, and building antibiotic resistance among both animals and humans.

In order to mitigate and combat infectious pathogens containing ARG, there are several mediations that are being explored and implemented.

DISCUSSION

There are many emerging therapies and prospective strategies that are being explored or implemented. Some of which will be discussed below.

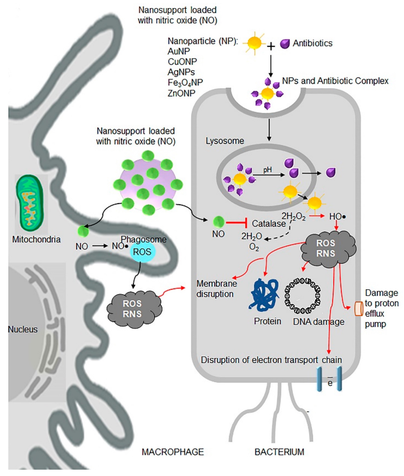
Table 4. Effect of essential oils against bacteria.

S.No.	Essential Oils (Components)	Active against Bacteria
1	Mentha (menthol, isomenthone, limonene, iso-menthanol, menthol acetate, carvone, β-pinene, α-pinene, 1,8-cineole, α-terpineol, isopulegol, pulegone, piperiton, piperitone oxide, and β-phellandrene.)	*S. aureus, Staphylococcus epidermidis, B. cereus,* and *E. coli, S. pyogenes, P. aeruginosa, Pseudomonas fluorescens, C. albicans,* and *V. cholerae*
2	Basil (Linalool, epi-α-cadinol, α-bergamotene, γ-cadinene, germacrene D, camphor. methylchavikol, methylcinnamat, linolen, eugenol, cis-geraniol, 1,8-cineole, α-bergamotene, β-caryophyllene, viridiflorol.)	*S. aureus* and *B. subtilis, Staphylococcus, Pseudomonas,* and *Enterococcus genera, L. monocytogenes* and *B. cereus Vibrio* spp. and *Aerobacter hydrophila*
3	Oregano (thymol, carvacrol, ρ-cymene, thymoquinone, and γ-terpinene.)	*Sarcina lutea, S. aureus, C. albicans, E. faecalis,* and *B. cereus*
4	Rosemary (α-pinene, myrcene, 1,8-cineole, camphor, camphene, α-terpineol, and borneol.)	*S. epidermidis, S. aureus, B. subtilis, Proteus vulgaris, P. aeruginosa,* and *E. coli.*

Essential oils are a type of secondary metabolites of aromatic plants. Liquid and volatile essential oils have significant medicinal properties in infectious and non-infectious diseases and have a low risk of antibiotic resistance.

Figure 4. Nanoantibiotics mechanism for ARGs

Principle of action by nano-antibiotic therapies including nitric oxide (NO) releasing nanoparticles and nanoparticles in combination with antibiotics is illustrated. In bacteria, NO leads to the production of harmful ROS and reactive nitrogen species (RNS) which are responsible for oxidative and nitrosative stress and death of bacteria.



CONCLUSION

Antibiotics became a part of modern medicine around seven decades ago and their efficacy and safety do not meet the demands of the intensifying animal production and growing human population, facing the global threat of infectious diseases. Experts from diverse fields such as clinical research, microbiology, genetic and computational engineering, imaging and modelling should work jointly to evolve strategies and develop novel therapeutics to address this problem.

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